DOT/FAA/AM-03/7

Office of Aerospace Medicine
Washington, DC 20591

Prevalence of Selective Serotonin Reuptake Inhibitors in Pilot Fatalities of Civil Aviation Accidents, 1990-2001

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May 2003

Final Report

This document is available to the public through the National Technical Information Service, Springfield, Virginia 22161.

U.S. Department of Transportation
Federal Aviation Administration

NOTICE

Technical Report Documentation Page

1. Report No.	2. Government Accession No.	3. Recipient's Catalog No.
DOT/FAA/AM-03/7		

Title and Subtitle	5. Report Date
Prevalence of Selective Serotonin Reuptake Inhibitors in Pilot Fatalities of Civil Aviation Accidents, 1990-2001	May 2003
	6. Performing Organization Code

7. Author(s)	8. Performing Organization Report No.
Akin A[1] and Chaturvedi AK[2]	

9. Performing Organization Name and Address		10. Work Unit No. (TRAIS)
[1]Gülhane Military Medical Academy Department of Aerospace Medicine Eskisehir 26020, Turkey	[2]FAA Civil Aerospace Medical Institute P.O. Box 25082 Oklahoma City, OK 73125	11. Contract or Grant No.

12. Sponsoring Agency name and Address	13. Type of Report and Period Covered
Office of Aerospace Medicine Federal Aviation Administration 800 Independence Ave., S.W. Washington, DC 20591	14. Sponsoring Agency Code

15. Supplemental Notes
This work was accomplished under the approved task AM-B-02-TOX-202.

16. Abstract
Selective serotonin reuptake inhibitors (SSRIs) are popularly prescribed for treating depression. With a few exceptions, these psychotropic medications are not approved by aeromedical regulatory authorities for use by aviators. Since SSRIs have the potential for impairing performance and causing drug-drug interactions, the prevalence of SSRIs in pilot fatalities of civil aviation accidents was evaluated. Postmortem samples from pilots involved in fatal civil aircraft accidents are submitted to the Civil Aerospace Medical Institute (CAMI) for toxicological evaluation. Findings from such evaluations are maintained in the CAMI Toxicology Database. This database was examined for the presence of SSRIs in pilot fatalities of the accidents that occurred during 1990-2001. Out of 4,184 fatal civil aviation accidents from which CAMI received samples, there were 61 accidents in which pilot fatalities had SSRIs. Of these accidents, 56 were of the general aviation category, 2 were of the air taxi and commuter category, 2 were of the agricultural category, and 1 was of the ultralight category. Blood concentrations of SSRIs in the fatalities were 11–1,121 $ng \cdot mL^{-1}$ for fluoxetine; 47–13,102 $ng \cdot mL^{-1}$ for sertraline; 68–1,441 $ng \cdot mL^{-1}$ for paroxetine; and 314–462 $ng \cdot mL^{-1}$ for citalopram. In 39 of the 61 pilots, other drugs—for example, analgesics, antihistaminics, benzodiazepines, narcotic analgesics, and/or sympathomimetics—and/or ethanol were also present. As determined by the National Transportation Safety Board, the use of an SSRI [with or without other drug(s) and/or ethanol] has been a contributory factor in at least 9 of the 61 accidents. Numbers of SSRI-involved accidents were low, and blood SSRI concentrations in the associated pilot fatalities ranged from subtherapeutic to toxic levels. However, the interactive effects of other drug(s), ethanol, and/or even altitude hypoxia in producing adverse effects in the pilots cannot be ruled out. Findings from this study should be useful in investigating SSRI- and other substance-involved accidents and in making decisions concerning the use of SSRIs in aviation.

17. Key Words	18. Distribution Statement
Forensic Sciences, Toxicology, Selective Serotonin Reuptake Inhibitors, Aviation Accident Investigation	Document is available to the public through the National Technical Information Service Springfield, VA 22161

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	22	

Form DOT F 1700.7 (8-72) Reproduction of completed page authorized

ACKNOWLEDGMENTS

The Government of Turkey is acknowledged for allowing the participation of Dr. Ahmet Akin in the FAA International Exchange Visitor Program at the FAA's Civil Aerospace Medical Institute (CAMI), Oklahoma City, OK.

The authors wish to thank Dr. Dennis V. Canfield of CAMI for his timely advice, valuable comments, and assistance in the data gathering process and the manuscript development. Without his support, this study would not have been possible. The authors are grateful to Patrick S. Cardona of CAMI for providing assistance in drawing the chemical structures of SSRIs and to Dr. John W. Soper and Dr. James E. Whinnery of CAMI for critically and enthusiastically reviewing the manuscript. Their comments and suggestions improved the quality of this report.

PREVALENCE OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN PILOT FATALITIES OF CIVIL AVIATION ACCIDENTS, 1990-2001

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs), a new generation of antidepressants, are effective medications for the treatment of depression (4,8). There are currently 5 drugs—fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram—classified as SSRIs (Figure 1). However, in the United States, fluvoxamine (Luvox®) is approved only for treating obsessive compulsive disorder (31). Fluoxetine was the first SSRI marketed in the United States in 1988, followed by other SSRIs. Since their availability (Table I), fluoxetine (Prozac®), sertraline (Zoloft®), paroxetine (Paxil®), and citalopram (Celexa®) have preferentially been prescribed because of low incidences of untoward adverse effects associated with their use, allowing these 4 SSRIs to remain in the top 200 drugs of the most dispensed prescriptions in the United States pharmaceutical industry (9,10,27,28,37-41,47-49). By being a part of the general population, aviators are subject to similar social pressures as other individuals of the society. Therefore, aviators have the potential for the need-based use of SSRIs, but these psychotropic medications are not approved by United States aeromedical regulatory authorities for use by aviators in order to avoid a possible compromise with aviation safety (15,20,22).

SSRIs are considered safe in comparison with other groups of antidepressants (6,30,44), though SSRIs have been linked to adverse effects primarily associated with the serotonin syndrome and drug metabolism inhibition (4,19,45). The former can be effectively treated, but the latter can lead to severe adverse effects in multi-drug users. All 5 SSRIs are extensively metabolized by the cytochrome P450 (CYP) enzyme system (4,17). Except for paroxetine and fluvoxamine, other SSRIs have active metabolites, as well (4,5,17). Fluoxetine, sertraline, their active

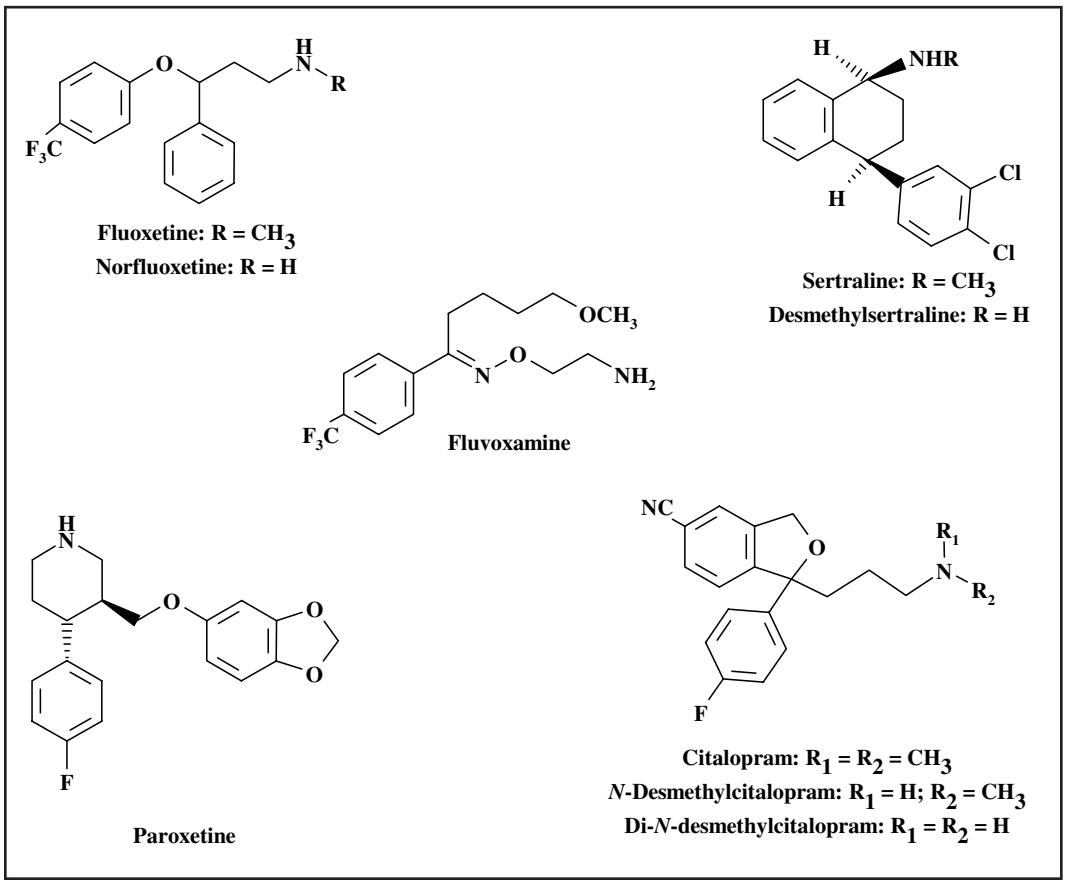

Figure 1: Chemical structures of selective serotonin reuptake inhibitors (SSRIs) and their active metabolites.

Table I. Rankings of Selective Serotonin Reuptake Inhibitors (SSRIs) in the Top-200 Drug Lists Based Upon the Total Prescriptions Dispensed in the United States Pharmaceutical Industry, 1990-2001

Year	Fluoxetine (Prozac®) [1988]*	Sertraline (Zoloft®) [1992]	Paroxetine (Paxil®) [1993]	Citalopram (Celexa®) [1998]
1990	16	–	–	–
1991	19	–	–	–
1992	17	148	–	–
1993	13	41	150	–
1994	9	20	53	–
1995	9	13	34	–
1996	7	11	24	–
1997	6	12	15	–
1998†	8	12	13	>20
1999	10	11	15	104
2000	13	10	14	53
2001‡	32	7	>10	>10

*Numbers within the brackets indicate the year in which the particular selective serotonin reuptake inhibitor (SSRI) was marketed in the United States.

†Only the top-20 drug list was published for this year (9).

‡Only the top-10 drug list was published for this year, with the exception of fluoxetine (47).

metabolites, paroxetine, and fluvoxamine inhibit certain CYP isoenzymes involved in the biotransformation of other drugs. Excluding citalopram, SSRIs inhibit their own metabolism by saturating their metabolizing CYP enzymes at higher SSRI (substrate) concentrations (17,19,33,34). Since patients with depression are frequently treated with multiple drugs, inhibition of the metabolism of these drugs by SSRIs can lead to drug-drug interactions, toxicity, and even death. Apparent association between the use of SSRIs and an increased risk of suicide has also been suggested in a few deaths (18,23,29,51). However, it should be remembered that the increased risk of suicide is an intrinsic risk of the disease itself (7,18). A study on the postmortem forensic toxicology of SSRIs has been published describing the cause and manner of death of 168 death-investigation cases (19). Fewer than 12 out of the 168 deaths were due to an intentional acute overdose of an SSRI on its own; however, the contributory role of an SSRI in the deaths resulting from overdoses of other drugs could not be ruled out primarily because of the drug metabolizing enzyme inhibitory properties of SSRIs.

Little is known about the postmortem aviation forensic toxicology of SSRIs. Since this field is basically a human-performance related postmortem forensic toxicology endeavor (42), findings on the prevalence of SSRIs in aviation accident pilot fatalities with the concentrations of SSRIs in the associated postmortem biosamples will be useful in the investigations of SSRI-associated aviation accidents. Such information will also be important to aeromedical regulatory authorities for making a possible future decision on the use of SSRIs by aviators. Therefore, the Civil Aerospace Medical Institute's (CAMI's) Toxicology Database (Oklahoma City, O.K.), the Federal Aviation Administration's (FAA's) National Aviation Safety Data Analysis Center (NASDAC) Database (Washington, D.C.), and the National Transportation Safety Board's (NTSB's) Aviation Accident Database (Washington, D.C.) were searched to obtain the applicable information. Findings from those database searches are presented in this study.

MATERIALS AND METHODS

Postmortem Pilot Forensic Toxicology Samples

During the investigation of aircraft accidents occurring within the jurisdiction of the United States, autopsied biological samples collected from pilot fatalities of civil aircraft accidents are submitted to CAMI for toxicological evaluation (3). Such sample submission is coordinated through the FAA's Office of Accident Investigation by the NTSB, which is responsible for investigating all United States civilian aircraft accidents. The collected samples are shipped to CAMI in the FAA's TOX-BOX evidence containers (14).

Toxicological Evaluation

The submitted pilot fatality biological samples are routinely analyzed for the presence of combustion gases (carbon monoxide and hydrogen cyanide), alcohol/volatiles, and drugs (11-14,43). All of these foreign substances (analytes) in the samples are analyzed according to established standard laboratory procedures, including screening and confirmatory/quantitative analyses (14). Analytes found in a pilot fatality case might not have necessarily been detected, or even analyzed, in each of the sample types submitted for toxicological evaluation from that particular accident pilot fatality. Analyses are dependent upon the nature of analytes, the sensitivity and specificity of analytical methods used, and the availability of sample types and amounts.

Drugs include a wide range of prescription, nonprescription, and illicit drugs. As with the majority of the drugs, SSRIs in the biosamples are screened by high performance liquid chromatography and by gas chromatography/mass spectrometry (GC/MS) and are confirmed/quantitated by GC/MS. Types and names of drugs found by CAMI during postmortem forensic toxicology of pilot fatalities associated with 1989-1993 and 1994-1998 civil aviation accidents have been published elsewhere (11,12).

Databases

Since 1990, toxicological findings of civil aircraft accident fatalities are electronically stored in a database maintained at CAMI. In the present study, this CAMI Toxicology Database was descriptively examined for the presence of SSRIs, with or without any other drug(s) and/or ethanol, in pilot fatalities of civil aviation accidents that occurred during a 12-year (1990-2001) period. Additionally, the database was searched to ascertain the number of 1990-2001 aviation accidents and associated pilot fatalities (cases) from which CAMI received postmortem biological samples. For this report, such aviation accidents are referred to as "CAMI accidents" and related pilot fatalities as "CAMI cases." Fatalities (cases) included in the present study consisted of only pilots—copilots are not included. Information on the types of airman certificates of those SSRI-associated pilots was retrieved from the CAMI Toxicology Database and from the NTSB Aviation Accident Database. The number of fatal aviation accidents reported by the NTSB for the 1990-2001 period was obtained from the FAA's NASDAC Database. The NTSB Aviation Accident Database was also used for obtaining information about the SSRI-related accidents, including the probable cause and/or factor(s) of those accidents, as determined and reported by the NTSB.

RESULTS

Fatal Civil Aviation Accidents

As reported in the FAA's NASDAC Database, the number of all the United States fatal civil aviation accidents for the 1990-2001 period was 5,449. Of these accidents, 4,570 were under the general aviation flight category (Title 14 CFR Part 91), 305 were under the air taxi and commuter flight category (Title 14 CFR Part 135), 168 were under the agricultural flight category (Title 14 CFR Part 137), 8 were under the ultralight flight category (Title 14 CFR Part 103), and the remaining 398 were under other flight categories (Table II). The Title 14 CFR Part 135 category included accidents of scheduled, as well as nonscheduled, flights. The NASDAC Database includes information primarily associated with the accidents of registered aircraft—information on the accidents of unregistered aircraft may not necessarily be included in this database.

CAMI Aviation Accidents and Pilot Fatalities

CAMI received postmortem biological samples for toxicological evaluation from 4,128 pilots (CAMI cases) associated with 4,184 fatal accidents (CAMI accidents) that occurred during the 12-year period (Table II). Out of these 4,184 accidents, 3,643 accidents with 3,611 pilot fatalities were related to general aviation flights, 220 accidents with 218 pilot fatalities were related to air taxi and commuter flights, 127 accidents with 127 pilot fatalities were related to agricultural flights, 44 accidents with 44 pilot fatalities were related to ultralight flights, and 150 accidents with 128 pilot fatalities were related to other categories of flights. The CAMI Toxicology Database includes both registered and unregistered aircraft accidents.

Table II. Operation Type-Based Comparative Categorization of 1990-2001 Fatal Civil Aviation Accidents Reported in the FAA' s National Aviation Safety Data Analysis Center (NASDAC) Database and in the CAMI's Toxicology Database

Operation Type*	FAA's NASDAC Database Accidents†	CAMI Toxicology Database‡		
		CAMI Accidents	CAMI Cases	CAMI SSRI-Related Accidents (Pilot Fatalities)
General aviation (Title 14 CFR Part 91)	4,570	3,643	3,611	56
Air taxi and commuter (Title 14 CFR Part 135)	305	220	218	2
Agricultural (Title 14 CFR Part 137)	168	127	127	2
Ultralight (Title 14 CFR Part 103)	8	44	44	1
Other operation types	398	150	128	–
Total	5,449	4,184	4,128	61

*Code of Federal Regulations (CFR), Title 14—Aeronautics and space, Chapter I, Subchapters F and G (16).

†May not include fatal accidents of unregistered aircraft.

‡Includes fatal accidents of registered, as well as unregistered, aircraft from which postmortem biological samples were submitted for toxicological evaluation. Such aviation accidents are referred to as "CAMI accidents" and related pilot fatalities as "CAMI cases." Details are also given in the text of the Materials and Methods section.

SSRI-Involved Aviation Accidents and Pilot Fatalities

Flight categories: Of the 4,184 CAMI accidents, SSRIs were found in 61 pilot fatalities (CAMI cases) associated with 61 aviation accidents (Table II). Of these 61 accidents, 56 involved general aviation flights, 2 air taxi and commuter flights, 2 agricultural flights, and 1 ultralight flight. Out of the 61 pilot fatalities, 22 had only SSRIs, and 39 also had other drug(s) and/or ethanol.

Airman certificate categories: Out of these 61 SSRI-involved pilots, 37 held private pilot certificates (36 United States private pilot certificate holders and 1 Canadian private pilot certificate holder), 13 held commercial pilot certificates, 4 held airline transport pilot certificates, 3 held student pilot certificates, and 1 held a recreational pilot certificate. The 3 remaining pilots were non-certified. Of the 37 private pilot certificate holders, 36 were involved in general aviation accidents, while 1 was involved in an ultralight accident. In the group of the 13 commercial pilot certificate holders, 9 were involved in general aviation accidents, 2 in air taxi and commuter accidents, and 2 in agricultural accidents. The remaining pilot fatalities—4 airline transport pilot certificate holders, 3 student pilot certificate holders, 1 recreational pilot certificate holder, and 3 non-certificated pilots—were involved in general aviation accidents.

Accidents and pilot fatalities: As is exhibited in Figure 2, there were no SSRI-associated pilot fatalities (cases) in the 1990 accidents, but the number of SSRI-involved fatalities increased from 1 in the 1991 accidents to 18 in the 2001 accidents. In the 12-year accidents, the highest number of pilot fatalities was associated with fluoxetine, which was first SSRI marketed in the U.S. in 1988. No fluvoxamine-associated pilot fatality was seen during the 12-year period. The trend of SSRI-involved pilot fatalities and associated accidents was consistent with the pattern of the SSRIs dispensed in the U.S. pharmaceutical industry during the 1990-2001 period (Figure 2; Table I).

Fluoxetine: This SSRI was found in 33 pilot fatalities (cases). In 13 cases, only fluoxetine and/or its primary active metabolite (norfluoxetine) were detected (Table

III)—blood, the toxicologically preferred sample type, was not available in 2 of these cases. Blood concentration ranges of fluoxetine and norfluoxetine were 61–1,121 ng·mL^{-1} and 52–1,388 ng·mL^{-1}, respectively. In the remaining 20 cases, other drugs—for example, analgesics, antihistaminics, benzodiazepines, narcotic analgesics, amphetamines and other sympathomimetics, cocaine and its metabolites, and/or tetrahydrocannabinol carboxylic acid—and/or ethanol were also detected (Table IV). Blood was not available in 6 of the 20 cases. Blood fluoxetine and norfluoxetine concentrations in those cases wherein other drugs and/or ethanol were present ranged from 11 to 778 ng·mL^{-1} and from 87 to 764 ng·mL^{-1}, respectively. Ethanol was found in only 3 cases—blood was not available in 1 of these cases. Blood ethanol concentrations in the 2 cases were 39 and 246 mg·dL^{-1}. Out of the 33 fluoxetine-involved cases, the use of the SSRI, with or without other drug(s), was determined by the NTSB to be a contributing factor in 7 accidents, of which 1 pilot fatality had only fluoxetine and norfluoxetine, while the remaining 6 pilot fatalities also had other drug(s). All of these 7 accidents were of the general aviation category. The cause/factor of 1 accident was undetermined, and the final reports of 3 accidents were not yet available in the NTSB database. The drug use was not reported to be a cause/factor in 22 of the 33 accidents by the NTSB.

Sertraline: Fourteen pilot fatalities (cases) had sertraline. In 4 cases, only sertraline and/or its active metabolite (desmethylsertraline) were detected (Table V). Blood concentration of this SSRI in 1 of the 4 cases was considerably high—sertraline: 13,102 ng·mL^{-1} and desmethylsertraline: 889 ng·mL^{-1}. In the remaining 10 cases, other drug(s) and/or ethanol were also detected (Table VI). Blood was not available in 1 of these 10 cases. In the 9 cases, the blood concentration range of sertraline was 47–1,860 ng·mL^{-1} and of desmethylsertraline it was 42–4,685 ng·mL^{-1}. Other drugs found in these 10 pilot fatalities were analgesics, sympathomimetics, diphenhydramine, and/or tramadol. Ethanol was found in 3 cases wherein no other drugs were detected—only sertraline was present. The NTSB determined the use of the SSRI, with other drug and/or ethanol, to be a contributing factor in 2 of the 14 sertraline-related accidents; both accidents were of the general aviation category. The

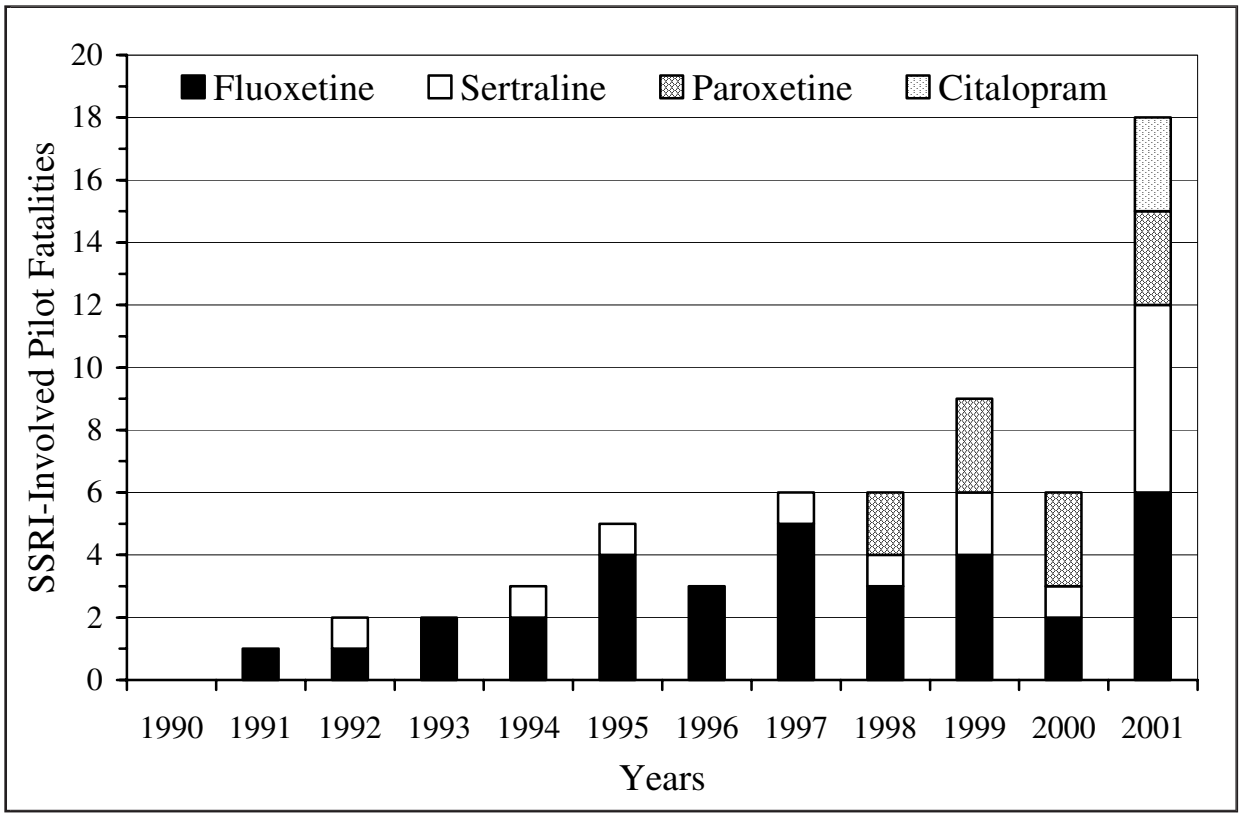

Figure 2: Numbers of selective serotonin reuptake inhibitor (SSRI)-associated pilot fatalities (CAMI cases) in civil aviation accidents that occurred during 1990-2001. Postmortem biological samples from the pilots of fatal aircraft accidents were submitted to CAMI for toxicological evaluation. Details are given in the text.

Table III. Fluoxetine and Norfluoxetine Found in Pilot Fatality (Case) Biological Samples Without Other Drugs and/or Ethanol

	Fluoxetine/Norfluoxetine ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$)			SSRI Use a Contributing Factor in the Accident per NTSB Report[*]
Case	Blood	Urine	Liver	
1	1,121/1,388	592/809	–[†]	Undetermined
2	200/300	–	6,200/15,000	Not mentioned
3	583/254	344/195	–	Not mentioned
4	ND[‡]/52	ND/D[§]	ND/155	Not mentioned
5	923/1,320	–	1,724/988	Not mentioned
6	61/D	–	20/ND	Not mentioned
7	ND/55	–	ND/1,182	Not mentioned
8	ND/ND	–	13/16	Not mentioned
9	211/861	–	10,161/36,277	Not mentioned
10	405/299	–	12,840/17,750	Yes (contraindicated drug-caused impaired judgment)
11	203/715	–	D/D	Not mentioned
12[¶]	Blood not available	–	700/1,500	Not mentioned
13[**]	Blood not available	–	31,000/74,000	Not mentioned

[*]As reported in the NTSB Aviation Accident Database at the time of the writing of this report.

[†]No data, because the sample type was either not available or not analyzed.

[‡]Not detected.

[§]Detected; no quantitative value.

[¶]Fluoxetine (200 $ng \cdot g^{-1}$) and norfluoxetine (200 $ng \cdot g^{-1}$) were also detected in kidney.

[**]Kidney contained 3,200 $ng \cdot g^{-1}$ fluoxetine and 18,000 $ng \cdot g^{-1}$ norfluoxetine, and lung contained 4,900 $ng \cdot g^{-1}$ fluoxetine and 56,000 $ng \cdot g^{-1}$ norfluoxetine.

Table IV. Fluoxetine and Norfluoxetine Found in Pilot Fatality (Case) Biological Samples with Other Drug(s) and/or Ethanol

Case	Samples	Fluoxetine/ Norfluoxetine ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$)	Other Drugs/Their Metabolites ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$) and/or Ethanol ($mg \cdot dL^{-1}$ or $mg \cdot hg^{-1}$)	SSRI Use [With Other Drug(s)/Ethanol] a Contributing Factor in the Accident per NTSB Report*
1	Blood	83/138	Temazepam (44)	Yes (prescription drug)
	Urine	D†/D	Temazepam (D)	
2	Blood	197/87	Amphetamine (D), methamphetamine (16)	Yes (drug-caused impairment)
	Urine	D/D	Amphetamine (229), methamphetamine (1,578)	
3	Blood	11/148	Nordiazepam (93), etomidate (D), lidocaine (D), atropine (D)	Not mentioned
	Liver	D/D	Nordiazepam (D), etomidate (D), lidocaine (100), atropine (D)	
	Kidney	D/43	–‡	
4	Blood	488/698	Phenylpropanolamine (D), ephedrine (D), pseudoephedrine (D), chlorpheniramine (148), chlordiazepoxide (D), nordiazepam (152), diltiazem (D), salicylate (8,000), acetaminophen (21,900)	Yes (drug-caused impairment of judgment and performance)
	Liver	D/D	Phenylpropanolamine (D), ephedrine (D), pseudoephedrine (D), chlorpheniramine (121), chlordiazepoxide (D), nordiazepam (D), diltiazem (D)	
	Lung	D/D	Phenylpropanolamine (D), ephedrine (D)	
5	Blood	89/101	Amphetamine (603)	Yes (medication-caused impairment)
	Urine	89/101	Amphetamine (7,816), carbamazepine (2,300)	
	Liver	98/100	Carbamazepine (4,400)	
6	Blood	778/764	Diphenhydramine (75), diltiazem (D)	Not mentioned
	Urine	D/D	Diphenhydramine (D), diltiazem (D), acetaminophen (9,300)	
7	Blood	293/333	Nordiazepam (D)	Not mentioned
	Urine	–	Temazepam (D), nordiazepam (31), oxazepam (D)	
	Liver	1,170/1,790	Nordiazepam (46), salicylate (69,800)	
8	Blood	642/676	Phenylpropanolamine (D), ephedrine (D), tetrahydrocannabinol carboxylic acid (D)	Not mentioned
	Urine	D/D	Phenylpropanolamine (D), ephedrine (D), tetrahydrocannabinol carboxylic acid (20), salicylate (215,500)	
	Liver	1,639/1,601	Phenylpropanolamine (D), ephedrine (D)	
9	Blood	367/185	Ephedrine (D)	Not mentioned
	Urine	73/33	Phenylpropanolamine (D), ephedrine (D), salicylate (31,000)	

Table IV. Fluoxetine and Norfluoxetine Found in Pilot Fatality (Case) Biological Samples with Other Drug(s) and/or Ethanol (continued)

Case	Samples	Fluoxetine/ Norfluoxetine ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$)	Other Drugs/Their Metabolites ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$) and/or Ethanol ($mg \cdot dL^{-1}$ or $mg \cdot hg^{-1}$)	SSRI Use [With Other Drug(s)/Ethanol] a Contributing Factor in the Accident per NTSB Report*
10	Blood§	D/209	Ethanol (246), pseudoephedrine (D), doxylamine (270), dextromethorphan (D), dextrorphan (D)	Not mentioned
	Urine	ND¶/109	Ethanol (220), phenylpropanolamine (D), ephedrine (D), pseudoephedrine (D), doxylamine (D), dextromethorphan (D), dextrorphan (D)	
	Vitreous fluid	–	Ethanol (289)	
11	Blood	43/242	Lidocaine (11,760), atropine (D)	Not mentioned
	Liver	2,252/D	–	
	Lung	–	Lidocaine (D), atropine (D)	
12	Blood	ND/400	Ethanol (39)	Final NTSB report not yet available
	Liver	D/D	–	
	Brain	–	Ethanol (36)	
	Muscle	–	Ethanol (55)	
13	Blood	–	Propoxyphene (172), norpropoxyphene (1,037)	Final NTSB report not yet available
	Liver	D/D	–	
	Kidney	D/D	Propoxyphene (2,240), norpropoxyphene (31,714)	
14	Blood	ND/296	Cocaine (10), benzoylecgonine (212), cocaethylene (D)	Not mentioned
	Liver	–	Benzoylecgonine (352)	
	Kidney	ND/D	–	
15**	Liver	7/109	Hydrocodone (496)	Yes (contraindicated drug)
	Kidney	D/24	Hydrocodone (D)	
16**	Liver	2,215/861	Cimetidine (D), diltiazem (D)	Yes (unapproved medication)
	Kidney	353/108	Cimetidine (D), diltiazem (D)	
17**	Liver	1,442/1,902	Desipramine (295), nordiazepam (251), phentermine (6,413), Bupropion (D), bupropion metabolite (D)	Not mentioned
	Kidney	448/582	Desipramine (97), nordiazepam (159), phentermine (3,486), Bupropion (D), bupropion metabolite (D)	

Table IV. Fluoxetine and Norfluoxetine Found in Pilot Fatality (Case) Biological Samples with Other Drug(s) and/or Ethanol (continued)

Case	Samples	Fluoxetine/ Norfluoxetine ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$)	Other Drugs/Their Metabolites ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$) and/or Ethanol ($mg \cdot dL^{-1}$ or $mg \cdot hg^{-1}$)	SSRI Use [With Other Drug(s)/Ethanol] a Contributing Factor in the Accident per NTSB Report*
18**	Liver	7/145	–	Not mentioned
	Kidney	8/26	Ethanol (164)	
	Muscle	–	Ethanol (15)	
19**	Liver	ND/201	Nordiazepam (269)	Not mentioned
	Kidney	ND/19	Nordiazepam (191)	
20**	Liver	D/D	Nordiazepam (D), verapamil (D), norverapamil (D)	Final NTSB report not yet available
	Kidney	–	Nordiazepam (D), oxazepam (D)	
	Muscle	ND/D	Verapamil (D), norverapamil (D)	

*As reported in the NTSB Aviation Accident Database at the time of the writing of this report.

†Detected; no quantitative value.

‡No data, because the sample type was either not available or not analyzed.

§Contained 12% carboxyhemoglobin.

¶Not detected.

**Blood not available.

Table V. Sertraline and Desmethylsertraline Found in Pilot Fatality (Case) Biological Samples without Other Drugs and/or Ethanol

	Sertraline/Desmethylsertraline ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$)				SSRI Use a Contributing Factor in the Accident per NTSB Report*
Case	Blood	Urine	Liver	Brain	
1	13,102/889	–†	587/330	985/1,311	Not mentioned
2	211/498	D‡/D	–	–	Not mentioned
3	D/83	D/D	D/D	–	Not mentioned
4	ND§/D	–	D/283	–	Final NTSB report not yet available

*As reported in the NTSB Aviation Accident Database at the time of the writing of this report.

†No data, because the sample type was either not available or not analyzed.

‡Detected; no quantitative value.

§Not detected.

pilot fatalities associated with these 2 accidents not only had sertraline and/or desmethylsertraline but also had diphenhydramine or ethanol. The drug use was not mentioned to be a cause/factor in 9 accidents by the NTSB, and the final reports of 3 accidents were not yet available in the NTSB database.

Paroxetine: As is given in Table VII, paroxetine was found in 11 pilot fatalities (cases). In 3 cases, only paroxetine was present. In the remaining 8 cases, other drugs—antihistaminics, sympathomimetics, alprazolam, butalbital, codeine, morphine, quinine, and/or verapamil—were also present. Ethanol was not detected in any of the 11 fatalities. Blood was not available in 3 of the 11 cases. The blood concentration range of paroxetine, with or without any other drug(s), was 68–1,441 $ng \cdot mL^{-1}$. The drug use was not established to be a cause/factor in 8 of the 11 accidents by the NTSB. The final reports of 3 accidents were not yet available in the NTSB database.

Citalopram: This SSRI was found in only 3 pilot fatalities (Table VIII). In 2 of these cases, only citalopram and its active metabolites—*N*-desmethylcitalopram and di-*N*-desmethylcitalopram—were detected, whereas acetaminophen and diphenhydramine were also detected in 1 case. Blood was not available in 1 case. Ethanol was not detected in any of the citalopram-related pilot fatalities. In accidents associated with 2 of these 3 cases, the drug use was not established to be a cause/factor by the NTSB; the final report of 1 accident was not yet available in the NTSB database.

DISCUSSION

Because SSRIs are popularly prescribed in the general population for effectively treating depression, and pilots are also a part of the population, there have been genuine concerns whether pilots should officially be granted permission to use SSRIs. Such a decision would require the assurance that SSRIs can be prescribed without compromising aviation safety. The SSRI-use-related safety issue was discussed in great detail at the 2002 Aerospace Medical Association (AsMA) scientific meeting (21,24,26,36,46,50). The reluctance of aeromedical regulatory authorities to allow the use of SSRIs by aviators primarily stems from the very basic pharmacological nature of SSRIs as being psychotropic drugs. These drugs have the potential to affect the central nervous system (CNS), thus might impair performance and ultimately compromise aviation safety. Because of these reasons, the FAA has been reluctant to approve the use of SSRIs by aviators.

Although pilots have the potential to use SSRIs, the presence of SSRIs in pilot fatalities is apparently less than expected, considering their heavy use in the general population (9,10,27,28,37-41,47-49), as only 61 SSRI-associated pilot fatalities were found out of the 4,128 pilot fatalities from the 4,184 CAMI accidents. The number of SSRI-associated pilot fatalities was higher in the general aviation flight category than in any other flight categories, which is consistent with the higher number of general aviation fatal accidents than the aviation

Table VI. Sertraline and Desmethylsertraline Found in Pilot Fatality (Case) Biological Samples with Other Drug(s) and/or Ethanol

Case	Samples	Sertraline/ Desmethylsertraline ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$)	Other Drugs/Their Metabolites ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$) and/or Ethanol ($mg \cdot dL^{-1}$ or $mg \cdot hg^{-1}$)	SSRI Use [With Other Drug(s)/Ethanol] a Contributing Factor in the Accident per NTSB Report*
1	Blood	283/ND†	Ethanol (156)	Yes (alcohol and drug-caused impairment of efficiency and judgment)
	Liver	D‡/ND	–§	
	Brain	–	Ethanol (107)	
	Bile	–	Ethanol (83)	
2	Blood	D/ND	Acetaminophen (16,200)	Not mentioned
	Liver	353/167	–	
	Heart	D/D	–	
3	Blood	564/186	–	Not mentioned
	Urine	ND/1,092	Phenylpropanolamine (D), pseudoephedrine (D)	
4	Blood	744/2,400	Acetaminophen (13,600)	Not mentioned
	Liver	2,700/5,200	–	
5	Blood	976/4,685	Pseudoephedrine (D)	Not mentioned
	Liver	17,199/54,121	Phenylpropanolamine (137), pseudoephedrine (5,797)	
6	Blood	49/42	Ethanol (398)	Final NTSB report not yet available
	Liver	D/D	–	
	Brain	–	Ethanol (259)	
	Vitreous fluid	–	Ethanol (405)	
7	Blood	1,860/1,772	Tramadol (5,716), salicylate (43,359)	Depression and inappropriate use of medication, as findings¶
	Liver	D/D	Tramadol (D)	
	Kidney	–	Tramadol (D)	

Table VI. Sertraline and Desmethylsertraline Found in Pilot Fatality (Case) Biological Samples with Other Drug(s) and/or Ethanol (continued)

Case	Samples	Sertraline/ Desmethylsertraline ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$)	Other Drugs/Their Metabolites ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$) and/or Ethanol ($mg \cdot dL^{-1}$ or $mg \cdot hg^{-1}$)	SSRI Use [With Other Drug(s)/Ethanol] a Contributing Factor in the Accident per NTSB Report*
8	Blood	1,672/2,983	Ethanol (55)	Final NTSB report not yet available
	Urine	D/D	Ethanol (78)	
	Liver	D/D	–	
	Brain	–	Ethanol (57)	
	Vitreous fluid	–	Ethanol (71)	
	Muscle	–	Ethanol (41)	
9	Blood	47/230	Diphenhydramine (251)	Yes (drug-caused impairment)
	Liver	D/D	Diphenhydramine (D)	
10**	Liver	23,239/49,573	Phenylpropanolamine (D), pseudoephedrine (D), ephedrine (D), diphenhydramine (1,157)	Not mentioned
	Kidney	3,727/10,133	Pseudoephedrine (D), diphenhydramine (213)	

*As reported in the NTSB Aviation Accident Database at the time of the writing of this report.

†Not detected.

‡Detected; no quantitative value.

§No data, because the sample type was either not available or not analyzed.

¶General aviation accident.

**Blood not available.

Table VII. Paroxetine Found in Pilot Fatality (Case) Biological Samples with or without Other Drug(s) and/or Ethanol[*]

Case	Samples	Paroxetine ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$)	Other Drugs/Their Metabolites ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$)	SSRI Use [With or Without Other Drug(s)] a Contributing Factor in the Accident per NTSB Report[†]
1	Blood	68	None detected	Not mentioned
	Urine	19	None detected	
2	Blood	96	None detected	Not mentioned
	Urine	D[‡]	None detected	
3	Blood	–[§]	–	Not mentioned
	Urine	D	Diphenhydramine (D), morphine (73), codeine (D), hydrocodone (72), dihydrocodeine (46)	
	Liver	228	Diphenhydramine (149)	
4	Blood[¶]	283	Pseudoephedrine (D)	Not mentioned
	Urine	D	Phenylpropanolamine (D), ephedrine (D), pseudoephedrine (D)	
5	Blood	374	–	Not mentioned
	Urine	1,040	Alprazolam (D), α-hydroxyalprazolam (D)	
6	Blood	1,441	Verapamil (D), norverapamil (D)	Final NTSB report not yet available
	Urine	D	Verapamil (D), norverapamil (D)	
7	Blood	619	Phenylpropanolamine (D), ephedrine (D), pseudoephedrine (D)	Final NTSB report not yet available
	Urine	D	Phenylpropanolamine (D), ephedrine (D), pseudoephedrine (D)	
8	Blood	355	–	Use of prohibited drugs, as a finding[**]
	Urine	D	Codeine (49), morphine (1,658)	
	Liver	D	–	
9[††]	Liver	1,608	None detected	Not mentioned
	Kidney	710	None detected	
10[††]	Liver	24,400	Diphenhydramine (6,240)	Not mentioned
	Muscle	208	–	
11[††]	Liver	D	Butalbital (681), quinine (D), Triprolidine (D)	Final NTSB report not yet available
	Muscle	–	Butalbital (241)	
	Heart	D	Quinine (D), triprolidine (D)	

[*]No ethanol was detected in this group of pilot fatalities.

[†]As reported in the NTSB Aviation Accident Database at the time of the writing of this report.

[‡]Detected; no quantitative value.

[§]No data, because the sample type was either not available or not analyzed.

[¶]Contained 17% carboxyhemoglobin and 0.31 $\mu g \cdot mL^{-1}$ cyanide.

[**]Air taxi and commuter accident.

[††]Blood not available.

Table VIII. Citalopram and its Metabolites Found in Pilot Fatality (Case) Biological Samples with or without Other Drugs and/or Ethanol*

Case	Samples	Concentration ($ng \cdot mL^{-1}$ or $ng \cdot g^{-1}$)				SSRI Use [With or Without Other Drug(s)] a Contributing Factor in the Accident per NTSB Report†
		Citalopram	*N*-Desmethyl-citalopram	Di-*N*-desmethyl-citalopram	Other Drugs/Their Metabolites	
1	Blood	314	157	11	None detected	Not mentioned
	Liver	D‡	D	650	None detected	
2	Blood	462	114	24	Diphenhydramine (194)	Final NTSB report not yet available
	Urine	D	D	D	Diphenhydramine (D), acetaminophen (17,406)	
3§	Liver	D	D	D	None detected	Not mentioned
	Kidney	D	D	D	None detected	

*No ethanol was detected in this group of pilot fatalities.

†As reported in the NTSB Aviation Accident Database at the time of the writing of this report.

‡Detected; no quantitative value.

§Blood not available.

accidents of other operation categories. This conclusion is supported by the observations that (i) 56 (92%) of the 61 SSRI-involved accidents and 3,643 (87%) of the 4,184 CAMI accidents were associated with the general aviation flights, (ii) all of the 9 accidents in which the use of an SSRI was determined to be a contributing factor were of the general aviation category, and (iii) the majority of the 61 pilots held airman certificates at the levels that authorized them for flying under the general aviation category.

The number of fatalities associated with an individual SSRI was consistent with its marketing year—for example, fluoxetine, marketed in 1988, was present in 33 pilot fatalities; whereas citalopram, marketed in 1998, was found in only 3 pilot fatalities. Although fluoxetine, sertraline, paroxetine, and citalopram were found in the 61 pilot fatalities, fluvoxamine was not detected in any of the total 4,128 CAMI aviation accident pilot fatalities. The absence of fluvoxamine in the pilot fatalities could be because this medication has not yet been approved in the U.S. for the treatment of depression—this drug is approved in the U.S. only for the treatment of obsessive compulsive disorder (31). Additionally, fluvoxamine is not a popularly prescribed medication—this drug has never been in the top-200 drug list of the most dispensed prescription drugs in the U.S. (9,10,27,28,47-49). The prevalence of fluvoxamine, in relation to other SSRIs, was also considerably low in a general forensic toxicology death investigation study consisting of 168 cases (19). In this study, fluvoxamine was present in only 5 death cases, whereas fluoxetine was found in 60 death cases, sertraline in 75 death cases, and paroxetine in 28 death cases.

SSRIs, themselves, may not exhibit considerable adverse effects on human performance at the recommended therapeutic doses, but depression, itself, has a significant potential for performance impairment. Nonetheless, because of the pharmacological potencies and drug metabolism inhibitory properties of SSRIs and their metabolites (4,5,17,19,45), SSRIs may adversely affect the CNS function and cause drug-drug interactions. Since SSRIs inhibit their own metabolism at high doses (17,19,33,34), the potential for the inhibition of the metabolism of other drugs is further increased in those cases wherein SSRIs are taken in high doses. Thus, SSRIs taken in conjunction with other drugs might interactively cause drug toxicity, even when other drugs are taken in therapeutic doses. Blood concentrations of those other drugs could be higher than their typical therapeutic blood levels because of the SSRI-caused inhibition of their metabolism, thereby their accumulation in blood.

Out of those 61 SSRI-associated pilot fatalities, 39 (64%) pilot fatalities also had other drug(s) and/or ethanol in their system. Some of the drugs—such as atropine, lidocaine, etomidate, and analgesics—found in the pilot fatalities could have been administered by emergency health care providers at accident scenes, or at hospitals, for resuscitation, pain reduction, and/or surgical procedures. Whereas, other drugs—such as antihistaminics, benzodiazepines, sympathomimetics, cardiovascular medications, and even abused drugs—and ethanol were very likely present in the system of the pilots prior to the accidents. Thus, pharmacodynamic and pharmacokinetic-level interactions of SSRIs and their active metabolites with other drug(s) and ethanol could realistically lead to performance impairment and unpredictable toxicopharmacological effects. Such performance impairment and adverse effects may well be increased at flying altitudes because of the reduced availability of oxygen to the brain and other organs.

Inhibition of their own metabolism is known to cause changes in the ratios of the parent SSRIs and their metabolites (17,19,33): These ratios are less at low SSRI doses in comparison with the ratios at high SSRI doses. Therapeutic serum level ranges of fluoxetine, sertraline, paroxetine, and citalopram are established to be 100–500, 25–50, 30–100, and 75–150 $ng{\cdot}mL^{-1}$, respectively (4). The relationship between the plasma (or serum) concentrations of SSRIs and their whole blood concentrations is not fully established, and the blood to plasma (or serum) concentration ratios of SSRIs may not necessarily be equivalent to 1. Therefore, the SSRI blood concentrations found in the present study may not truly represent their plasma or serum levels. Although therapeutic, toxic, and lethal levels of SSRIs in whole blood are not clearly determined based on the postmortem forensic toxicology of death investigation cases, the lowest blood levels determined to have resulted in death were 630 $ng{\cdot}mL^{-1}$ for fluoxetine; 1,500 $ng{\cdot}mL^{-1}$ for sertraline; and 400 $ng{\cdot}mL^{-1}$ for paroxetine (19). Anastos et al. (1) have concluded therapeutic and lethal concentrations of citalopram in blood to be 400 $ng{\cdot}mL^{-1}$ and 800 $ng{\cdot}mL^{-1}$, respectively. The majority of pilot fatality blood SSRI levels, in the absence of other drug(s) and/or ethanol, observed in the present postmortem aviation forensic toxicology study fell below, or close to, the reported values in the death investigation cases (1,19). The blood sertraline concentration of 13,102 $ng{\cdot}mL^{-1}$ found in 1 of the pilot fatalities (Table V) is approximately 4-fold higher than the upper blood value of the sertraline concentration range reported in the 75 sertraline-related death investigation case study (19). Therefore, the 13,102 $ng{\cdot}mL^{-1}$ blood sertraline level could be considered as a supra-toxic or lethal concentration. Reaching such a high concentration in blood could be attributed to (i) the intentional ingestion of a

considerable amount of the SSRI, (ii) the contamination of the postmortem blood sample by the gastrointestinal track (GI) contents, and/or (iii) the postmortem redistribution of the SSRI among various body compartments, particularly from a higher concentration gradient of the SSRI in the GI track to a lower concentration gradient of the SSRI in the blood compartment.

Including sertraline, SSRIs are chemically basic drugs, and extensive postmortem redistribution has been reported with basic drugs (2,32,35). Therefore, blood concentrations of SSRIs found after death may not necessarily represent their antemortem blood levels. In view of this, during the investigations of aviation accidents involving SSRIs, the postmortem blood levels of SSRIs should be carefully evaluated and interpreted, particularly when other drug(s) and/or ethanol are also present. As is true with any drug, in the 13 pilot fatalities wherein the toxicologically preferred sample—blood—was not available, levels of SSRIs in other biological sample types cannot be correctly correlated with the degree of performance impairment or adverse effects, since such levels merely indicate the exposure of those victims to SSRIs.

The NTSB has determined "the use of drug" as a contributing factor in at least 9 (15%) out of the 61 SSRI-related accidents, which does not necessarily imply only SSRIs—this may also very well refer to other drug(s) and/or ethanol present in those accident-related pilots. Final NTSB reports of 10 out of those 61 accidents are not yet available in the public domain database. Once those reports are finalized, the number of accidents wherein the use of an SSRI, with or without other drug(s) and/or ethanol, was a contributing factor may increase.

The low number of SSRI-associated pilot fatalities has a realistic practical relevance, especially when SSRIs have been a popularly prescribed group of medications in the U.S. (9,10,27,28,37-41,47-49). Ideally, considering the prohibition for use of SSRIs by aviators, an SSRI should not have been found in any pilot fatality. The SSRI-related 61 pilots were identified only because those pilots were victims of fatal accidents and their postmortem samples were toxicologically evaluated. Even though contributing roles of weather conditions, mechanical deficiencies, and/or piloting errors cannot be completely ruled out in the 61 accidents, this number is of concern with reference to aviation safety. This concern is further deepened by the fact that the 61 SSRI-associated accidents are 12% of the total (505) prescribed-medication related 1990-2001 CAMI accidents, particularly realizing that this percentage represents only 4 prescription drugs. On the other hand, the number of SSRI-associated pilots is a fraction of the pilot population and may not necessarily represent the true spectrum of the usage of SSRIs in aviators. Therefore, a well-designed population study on pilots could reveal a much higher usage of SSRIs in pilots, as reflected during a presentation at the 2002 AsMA scientific meeting (21) and during an FAA aviation medical examiner seminar (25).

CONCLUSIONS

Findings from the present study clearly suggest low numbers of accidents wherein drug use was determined to be a contributing factor and/or wherein pilot fatalities had SSRIs in the presence or absence of other drug(s) and/or ethanol. Nevertheless, the absolute number of SSRI-related accidents and associated fatalities cannot be condoned. In the upcoming years, the number of SSRI-associated fatal aviation accidents may potentially increase as the use of SSRIs in the general population, including pilots, increases as a function of time. Information on the prevalence of SSRIs in aviation accident pilot fatalities along with SSRI concentrations in biological samples will continue to be useful in the investigations of accidents wherein SSRIs and other substances are involved. Additionally, findings from this study should guide future research and be utilized in making a possible future decision concerning the use of SSRIs by aviators.

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